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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,005	10/02/2003	Norman L. Anderson	ANDE-001/04US 307109-2001	6420

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
10/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,005	ANDERSON, NORMAN L.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44,47-61,64,65,67 and 71-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,47-61,64,65,67 and 71-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/22/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 22, 2007 has been entered.

Amendment Entry

2. The amendment July 10, 2006 has been entered. The examiner acknowledges the amendment to the specification. Claims 1-43, 45-46, 62-63, 66, and 68-70 have been cancelled. Claims 73-80 have been newly added. Claims 44, 47-61, 64-65, 67 and 71-80 are under consideration in this office action.

Withdrawal of Rejections

3. The following objections and rejections have been withdrawn in view of applicants' amendments and arguments:

a) The rejection of claims 44-47, 52-60, 67 and 71-72 under 35 U.S.C. 102(b) as anticipated by Geng et al. (J. of Chromatography A, 2000, Vol. 870: page 295-313);

b) The rejection of claims 48-49, 61, 62-66 and 68 under 35 U.S.C. 103(a) as being unpatentable over Geng et al., (J. of Chromatography A, 2000, Vol. 870: page 295-313) in view of Zhao et al. (PNAS. 1996. Vol. 93:4020-4024); and

c) The rejection of claims 44-72 under 35 U.S.C. 112, second paragraph.

Response to Arguments

4. Applicant's arguments filed May 22, 2007 have been fully considered but they are not persuasive. Applicant's arguments with respect to claim 44, 47-61, 64-65, 67 and 71-80 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection Necessitated By Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 44, 47-61, 64-65, 67 and 71-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geng et al. (J. of Chromatography A, 2000, Vol. 870: page 295-313) in view of Nelson et al., (1995. Ana. Chem).

The claims are drawn to a method of quantifying an amount of at least a first monitor peptide and a second monitor peptide in a biological sample, the first monitor

peptide and the second monitor peptide being produced by digestion of a first protein and a second protein, respectively, by a proteolytic agent, the product of the digestion of the biological sample being a digested sample, comprising: binding the first monitor peptide to a first binding agent, the first binding agent being a polyclonal antibody; and binding a labeled version of the first monitor peptide to the first binding agent, the labeled version of the first monitor peptide being present at a known amount in the digested binding the second monitor peptides to a second binding agent, the second binding agent being different from the first binding agent; binding a labeled version of the second monitor peptide to the second binding agent, the labeled version of the second monitor peptide being present at a known amount in the digested sample; the first monitor peptide bound to the first binding agent, the labeled version of the first monitor peptide bound to the first binding agent, the second monitor peptide bound to the second binding agent and the labeled version of the second monitor peptide bound to the second binding agent being bound peptides, peptides produced by the digestion of the biological sample not bound to the first binding agent or the second binding agent being unbound peptides, separating bound peptides from unbound peptides; and measuring the amount of the first monitor peptide that was separated from-unbound peptides using a mass spectrometer; measuring the amount of the labeled version of the first monitor peptide that was separated from unbound peptides; calculating the amount of the first monitor peptide in the biological sample; measuring the amount of the second monitor peptide that was separated from unbound peptides; measuring the amount of the labeled version of the second monitor peptide that was separated from

unbound peptides; and calculating the amount of the second monitor peptide in the biological sample.

Geng et al., teach signature peptide approaches to detecting proteins in complex mixtures. Geng et al., teach the sample was digested (page 298). Geng et al., teach classes of peptide fragments were selected by affinity chromatography using different lectin columns (abstract). Geng et al., teach proteins in complex mixtures were digested to create classes of peptide fragments (abstract). Geng et al., teach the digested samples were injected onto the column (page 298). Geng et al., teach several purification techniques were disclosed, including serial lectin affinity columns, anion-exchange chromatography, metal affinity chromatography or capillary electrophoresis as being used to separate the fractionated peptides (page 299). The digested human serotransferrin was injected onto affinity column (page 296). Geng et al., teach affinity selection was also performed affinity columns (page 298). Geng et al., teach the analytes displaced from the column were then eluted (page 298). Geng et al., teach silica based columns, thereby teaching monolithic porous beads as the support (pages 298 and 300). Geng et al., teach sequential loading and elution of the products (page 298). Geng et al., teach a wash of the column, which removed unbound analyte (page 298). Figure 4(b) shows two glycopeptides isolated from the ConA column. Geng et al., teach the eluted peptides were monitored and fractions were collected for MALDI-time of flight mass spectrometry analysis (MALDI-TOF-MS) (page 298). The equations were deduced from the ratios of deuterium-labeled and unlabeled acetylated peptides (page 299). Figure 7 of Geng et al., shows signature peptides having masses at different

peaks. Figures 5 and 7 show mass spectrum results from a first and second glycopeptides.

Geng et al., teach the synthesis of *N*-acetoxysuccinamide, *N*-acetoxysuccinamide and d_3-C^1 N-acetoxysuccinamide as different isotopic labels added to the peptides (page 298). Geng et al., teach at least two differently labeled peptides being prepared and loaded onto the support system and mass spectrometer. The MALDI-TOF-MS was performed using a mass spectrometer (page 298). Geng et al., show data teaching proteins being quantified as signature peptides using isotopically labeled internal standards or monitor peptides. Geng et al., teach this is based on the concept of using and adding the mixture a very similar, but distinguishable substances and determining the concentration of analyte relative to a known concentration of the internal standard (page 308). Geng et al., teach the signature peptides and monitor peptides are all generated by trypsin digestion (page 308). Figure 9(a) depicts the mass spectrum of the labeled and unlabeled peptide. Geng et al., teach isotopes ratios of peptides were determined by MALDI-MS and used to determine the concentration of a peptide relative to that of the labeled internal standard peptides (abstract). Geng et al., teach a method for quantifying the amount of a target protein in a biological sample. The proteins in complex mixtures were digested with a proteolytic agent to create classes of peptide fragments. The digested samples thereby creating a mixture were injected onto the affinity column (page 298). The eluted peptides were monitored and fractions were collected for MALDI-time of flight mass spectrometry analysis (page 298). The equations were deduced from the ratios of deuterium-labeled and unlabeled acetylated

peptides (page 299). Geng et al., teach measuring the amount of the monitor peptides using a mass spectrometer.

However Geng et al do not teach the use of polyclonal antibodies as binding agents.

Nelson et al., teach detection of antigens by Matrix Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOFMS) using polyclonal antibodies (page 1153). Mass spectrometric immunoassay (MSIA) principles are taught by the authors (page 1153). Nelson et al., teach immunoaffinity capture and mass spectrometry are separate yet have complementary roles during Mass spectrometric immunoassay (page 1153). Nelson et al., teach affinity capture is necessary to overcome signal suppression and matrix saturation effects typically encountered during direct MALDI analysis of complex biofluids and to increase molar sensitivity by concentration the antigen into a small volume (page 1153). Nelson et al., teach mass spectrometry is used for rapid, sensitive and highly specific detection of the affinity captured species (page 1154). Moreover, Nelson et al., teach the most obvious benefit is the ability to screen for multiple antigens in a single assay (page 1154). Nelson et al., teach using MSIA reagents prepared with multiple antibodies, a number of antigens can be retrieved from solution and unambiguously determined in a single mass spectrum (page 1154). The multiple antigen analysis affords a dimension of specificity beyond that of conventional assays (page 1157).

It would have been prima facie obvious at the time applicants' invention to modify the method of quantifying an amount of at least a first monitor peptide and a second

monitor peptide in a biological sample as taught by Geng et al., to incorporate mass spectrometry detection using polyclonal antibodies as taught by Nelson et al., because Nelson et al., already teach the use of polyclonal antibodies to capture and detect antigens by mass spectrometry and such incorporation provides rapid, sensitive and highly specific detection of the affinity captured species. One would have a reasonable expectation of success because no more than routine skill would have been required to incorporate a polyclonal antibody to bind an antigen when antibodies are well known in the art to capture antigens and to be used in conjunction with mass spectrometry analysis to increase molar sensitivity by concentration the antigen into a small volume. Furthermore, no more than routine skill is required to use the mass spectrometry techniques, since MSIA has high-level specificity offering a high level of immunity to ambiguities arising from nonbiospecific adsorption. Moreover, the incorporation of mass spectrometry is desirable based on the fact that immunoaffinity capture and mass spectrometry have complementary roles; and affinity capture is necessary to overcome signal suppression. Furthermore, one having ordinary skill in the art would have been motivated to make such changes concerning the total mass since only the expected results would have been obtained. Therefore routine optimization, like adjusting the amounts of unbound peptides is not patentable since changes in amounts of an old process do not impart patentability in order to achieve the results taught in the prior art.

Conclusion

6. No claims allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew, can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
August 31, 2007

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Ja-Na Hines
August 31, 2007

MARK NAVARRO
PRIMARY EXAMINER